Inactivation of Msx1 and Msx2 in neural crest reveals an unexpected role in suppressing heterotopic bone formation in the head.

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Public Summary:
The growth of the vertebrate skull is a complex and as yet poorly understood process that involves the migration of several distinct cell populations, including neural crest cells, which migrate from the neural tube to the developing skull. In the present study, as part of an effort to understand more fully how the bones of the skull are shaped, we inactivated the developmental regulatory genes, Msx1 and Msx2, in neural crest cells. We found that inactivation of up to 3 of 4 alleles or copies of Msx1/2 resulted in a large defect in the skull. Inactivation of all four alleles unexpectedly, caused the large defect to be filled with bone. This bone originates from cells that normally do not form bone. Thus Msx1 and Msx2 have two roles in skull development: they are needed for the growth of skull bones, and they are also needed to prevent the formation of bone in a normally non-bone forming cell type.

Scientific Abstract:
In an effort to understand the morphogenetic forces that shape the bones of the skull, we inactivated Msx1 and Msx2 conditionally in neural crest. We show that Wnt1-Cre inactivation of up to three Msx1/2 alleles results in a progressively larger defect in the neural crest-derived frontal bone. Unexpectedly, in embryos lacking all four Msx1/2 alleles, the large defect is filled in with mispatterned bone consisting of ectopic islands of bone between the reduced frontal bones, just anterior to the parietal bones. The bone is derived from neural crest, not mesoderm, and, from DiI cell marking experiments, originates in a normally non-osteogenic layer of cells through which the rudiment elongates apically. Associated with the heterotopic osteogenesis is an upregulation of Bmp signaling in this cell layer. Prevention of this upregulation by implantation of noggin-soaked beads in head explants also prevented heterotopic bone formation. These results suggest that Msx genes have a dual role in calvarial development: They are required for the differentiation and proliferation of osteogenic cells within rudiments, and they are also required to suppress an osteogenic program in a cell layer within which the rudiments grow. We suggest that the inactivation of this repressive activity may be one cause of Wormian bones, ectopic bones that are a feature of a variety of pathological conditions in which calvarial bone development is compromised.